

Upper Extremity Deep Vein Thrombosis: Symptoms, Diagnosis, and Treatment

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ABSTRACT: Upper extremity deep vein thrombosis (UEDVT) is defined as thrombosis of the deep venous system (subclavian, axillary, brachial, ulnar, and radial veins), which drains the upper extremities. It can be caused by thoracic outlet anatomic obstruction, such as Paget–Schroetter syndrome, (primary) or by central intravenous catheters (secondary). UEDVT may be asymptomatic or present with acute severe pain and arm swelling. Clinical suspicion should be confirmed by diagnostic imaging procedures such as duplex ultrasound, computed tomography scan, or magnetic resonance imaging. UEDVT is managed by anticoagulant treatment. In addition to that, early thrombolysis aimed at preventing post-deep vein thrombosis syndrome and thoracic outlet decompression surgery should be given to patients with primary UEDVT. Anticoagulation without thrombolysis is the treatment of choice for patients with catheter-related thrombosis. Mandatory functioning catheters can remain in place with anticoagulant treatment. All other catheters should be immediately removed. The management of patients with UEDVT requires an experience multidisciplinary team comprised of internists, radiologists, hematologists, and vascular surgeons. Understanding the risk factors for the development of UEDVT, the diagnostic procedures, and the treatment modalities will improve the outcome of those patients.

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KEY WORDS: upper extremity deep vein thrombosis (UEDVT), central intravenous catheter, thoracic outlet anatomic abnormality, thrombolysis, pharmacomechanical thrombectomy

Upper extremity deep vein thrombosis (UEDVT) is a rare disorder and much less common than lower extremity DVT. It may be classified as primary (thoracic outlet compression) or secondary (mainly catheter related). The complications and management of UEDVT depend on the cause of the DVT (primary or secondary). In the present review we discuss the diagnostic and therapeutic approach for the management of UEDVT.

CLASSIFICATION OF UEDVT

Primary UEDVT (Paget–Schroetter syndrome) was originally described by James Paget in 1875 and Leopold van Schrötter in 1884. It is defined as UEDVT due to anatomic abnormalities

of the thoracic outlet and accounts for about 20% of all cases of UEDVT [1]. Anatomic structures compressing the veins that pass through the thoracic outlet can cause stasis, which leads to UEDVT. Thus, primary UEDVT is also called venous thoracic outlet syndrome [2]. Compression of the upper extremity veins can occur at the costoclavicular space or at the scalene triangle. The anatomic abnormalities that compress the upper extremity veins can be congenital (e.g., accessory rib, abnormal scalene tendon insertion, supernumerary muscle and tendons) or acquired (e.g., bone fracture, subclavian muscle hypertrophy) [3,4]. It can be unilateral or bilateral [5]. Interestingly, right primary UEDVT is more common than left primary UEDVT due to the greater usage of the right hand, most people are right-handed [1]. The median age of diagnosis of primary UEDVT is 30–5 years with a male to female ratio of 2:1 [1]. UEDVT occurs more often in the subclavian vein (18–67%), followed by the axillary vein (5–25%) and brachial vein (4–11%) [6].

Secondary UEDVT accounts for the majority (80%) of all cases of UEDVT. The main causes for secondary UEDVT are intravenous catheters, pacemakers, malignancy, or thrombophilia [7,8]. As such, most patients with secondary UEDVT are much older than primary UEDVT patients [9].

EPIDEMIOLOGY

The annual incidence of UEDVT is about 1/100,000 or 2/100,000. It accounts for only 1–4% of all DVT events; as most of the DVT occurs in the lower extremities [10]. UEDVT is less common than lower extremity DVT because of the relatively high blood flow in upper extremities and the lack of stasis.

Risk factors for primary UEDVT include young age, strenuous upper extremity exercise, and repetitive overhead hyper abduction with thoracic outlet anatomic abnormality [1]. The incidence of UEDVT in patients with central catheters is not known. It depends on catheter size, catheter location and the nature of the patients (higher risk in patients with thrombophilia or malignancy) [9,11]. Using ultrasound to screen asymptomatic patients with central catheter demonstrated the presence of UEDVT in about 10% of the patients [12]. Risk factors for catheter related UEDVT include catheter malposition, large size catheters, peripherally insertion of central catheter, catheter infection, prothrombotic status, malignancy, and chemical irritation (e.g., chemotherapeutic agents) [9,11].

CLINICAL MANIFESTATIONS

Acute UEDVT usually presents with arm pain and swelling. Other symptoms and signs may include shoulder, neck, or axilla discomfort; superior vena cava syndrome; cyanosis of the hand and fingers; low grade fever; and signs of superficial vein thrombosis [13]. Occasionally, especially in cases with partial UEDVT, the pain and swelling may be minimal (or even absent) and the major findings are collateral subcutaneous veins over the proximal part of the arm or at the upper chest wall (Urschel's sign) [12]. Clinical pulmonary embolism (PE) with shortness of breath occurs in patients with UEDVT at much lower rates (4–10%) compared to that observed in patients with lower extremity DVT [14]. Nevertheless, subclinical PE can be detected in up to 33% of the patients with UEDVT [15]. PE, although uncommon, may be the presenting and the major symptom in patients with UEDVT [13,14]. Post-thrombotic syndrome is defined as venous insufficiency that occurs as a result of damaged venous valves that leads to pain and swelling of the involved extremity. It develops in up to 50% of patients with UEDVT [16]. Post-DVT syndrome is much more common in patients with primary UEDVT (compared to secondary UEDVT), especially in patients who were not treated with thrombolysis and/or with surgical decompression [16]. Usually there is no clinical impairment of arteries or peripheral nerves in the affected limb unless there is significant edema and compression of the nerves and/or arteries [17].

DIAGNOSIS

As for lower extremity DVT, clinical history and physical examination are essential for the diagnosis of UEDVT [8]. The D-dimer test is used to rule out thrombosis with a high negative predictive value [18]. The yield of the physical examination in the diagnosis of UEDVT is quite low [18]. Therefore, imaging techniques should be used. Ultrasound (B-mode ultrasound, duplex and color Doppler ultrasound) is the preferred initial imaging technique for the diagnosis of UEDVT with high sensitivity (84–97%) and specificity (93–96%) [19,20]. It is simple, available, noninvasive, and reliable without radiation or injection of nephrotoxic contrast media. Nevertheless, ultrasound has several disadvantages. The interpretation of ultrasound is dependent on the operator, thus an inexperienced operator may miss the correct diagnosis [19,20]. In addition, ultrasound is not a good imaging test for proximal subclavian or the innominate veins due to acoustic shadows from the surrounding bones [21]. Digital subtraction venography can define the upper extremity venous anatomy better than ultrasound; therefore, it is considered the gold standard test for UEDVT diagnosis. It is indicated when ultrasound studies are

Upper extremity deep vein thrombosis (UEDVT) can be primary (thoracic outlet obstruction) or secondary (mainly due to central catheter)

not conclusive, especially in cases with high clinical suspicion of UEDVT [19,22]. However, the necessity for contrast media injection in the later imaging technique limits its usage in many patients. Computed tomography (CT) or magnetic resonance imaging (MRI) are preferred for patients with suspected

UEDVT in whom ultrasound studies are not conclusive and digital subtraction venography is contraindicated. Another advantage of CT and MRV is the ability to

identify underlying anatomic abnormalities and thoracic outlet obstructions (e.g., malignancy) [23,24].

MANAGEMENT

The goals of treatment for UEDVT are the relief of the acute symptoms caused by the obstruction of the veins, the prevention of UEDVT complications (e.g., pulmonary embolism, post-thrombotic syndrome), and the prevention of recurrences. Long-term prospective randomized clinical trials of patients with UEDVT are lacking. Therefore, there is no consensus regarding the optimal treatment of UEDVT. Supportive treatment should be offered to all patients with UEDVT. This treatment consists of elevation of the relevant extremity, rest, analgesia, and gradual compression. In cases of infection, local and/or systemic antibiotic treatment should be given [25].

TREATMENT OF PRIMARY UEDVT:

Apart from the supportive care, anticoagulation with low-molecular-weight heparin or fondaparinux followed by vitamin K antagonists for 3–6 months should be given to all patients with UEDVT unless it is contraindicated [26]. For patients with recurrent UEDVT or thrombophilia, lifelong anticoagulation should be considered. In patients who have contraindications for anticoagulation treatment, percutaneous filter (umbrella) insertion into the superior vena cava (SVC) may be considered. Umbrella insertion can prevent pulmonary embolism, but has no effect on the thrombus itself and cannot prevent post-thrombotic syndrome [27].

Currently, due to the uncertain benefits of SVC filters, these filters are rarely used. SVC filters should be reserved for specific patients who have no other therapeutic options [20]. Anticoagulation alone may be appropriate for patients who present

Early thrombolysis and thoracic outlet decompression in addition to anticoagulation is indicated in primary upper extremity deep vein thrombosis (UEDVT)

more than 2 weeks after symptoms initiation (chronic UEDVT) or for patients with very mild symptoms [26]. For all other primary UEDVT patients, catheter-based thrombolytic treatment should be given, taking into consideration

the risk of bleeding in high risk patients [28,29]. The aim of the thrombolytic therapy is to dissolve the thrombus, to minimize endothelial injury, to reduce inflammation, and to restore the thrombotic vein patency [26]. Achieving those goals should

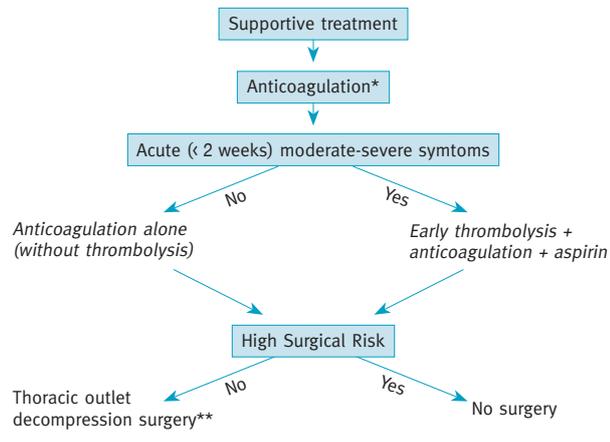
prevent the development of post-thrombotic syndrome. Indeed, thrombolytic treatment decreases the rate of post-thrombotic syndrome by 60% compared to treatment with anticoagulation alone [29]. To be effective, thrombolytic therapy should be initiated early, within 24 hours of diagnosis. Thrombolysis administered via catheter placed in the basilic vein is much better than systemic thrombolysis, because it leads to higher rates of vein patency with lower risks of bleeding [29]. The preferred agent is alteplase, given at a rate of 0.01 mg/kg/hour up to a total dose of 20–25 mg. The average duration of thrombolytic treatment is 24 to 72 hours, depending on the extent and burden of thrombus [30]. Other agents such as urokinase, streptokinase, tissue plasminogen activator (tPA), or reteplase can also be used [30]. Since the thrombolytic therapy may lead to platelets activation, it should always be accompanied by both anticoagulation and aspirin [30]. Unfractionated heparin is preferred over LMWH as the anticoagulant agent in patients treated with thrombolysis because of the rapid dose adjustments [30]. Assessment of vein patency by venography 12–24 hours following thrombolytic therapy is indicated to consider continuation of thrombolytic treatment if the thrombus did not properly dissolve [29,30].

Surgical thoracic outlet decompression should be considered in all patients with primary UEDVT with low surgical risk [31–33]. It should be performed as soon as possible but not earlier than 2 hours after the termination of thrombolytic therapy. When the specific abnormality causing the thoracic outlet obstruction is identified (e.g., cervical rib, anomalous thoracic outlet band, anomalous musculotendinous insertion) surgery should be targeted to correct it (e.g., resection of cervical rib) [31]. When no clear anatomical obstructive abnormality can be identified, rib resection should be considered, especially in patients with recurrent UEDVT. During surgery, additional potential causes of venous compression may be identified and managed [33]. The thoracic outlet decompression surgical procedures are relatively safe, but complications such as pneumothorax, hemothorax, brachial plexus injury, long thoracic nerve injury, and arterial injury may occur in about 1–2% of patients [34] [Figure 1].

Recently, percutaneous mechanical thrombectomy (PMT) aimed to remove the thrombus was shown to be highly effective in the treatment of UEDVT. PMT can be conducted by high velocity jet (e.g., AngioJet, Possis Medical, Minneapolis, MN, USA) or by mechanical dispersion wire (e.g., Trellis-8, Bacchus Vascular, Santa Clara, CA, USA). PMT can be used alone or with pharmacologic catheter-based thrombolysis (pharmacomechanical thrombolysis). The major adverse event of the latter treatment is bleeding in 3–4% of the treated patients [20].

Another therapeutic option is balloon angioplasty with stenting. Data regarding the efficacy of stent insertion for the treatment of UEDVT is limited. It seems that stents occlusion rates 6–24 months following its insertion are quiet common [35].

Figure 1. Therapeutic approach for primary upper extremity deep vein thrombosis (UEDVT). Supportive treatment should be offered to all patients



*Anticoagulation should be given to all patients with primary UEDVT for 3–6 months unless it is contraindicated (consider umbrella insertion). Anticoagulation should be given for 3–6 months regardless of whether thrombolysis and/or thoracic outlet decompression surgery are performed
 **Surgical thoracic outlet decompression should be offered shortly following thrombolysis. In case of delay thoracic outlet decompression surgery, anticoagulation should be continued until the surgical procedure is done

Thus, currently the role of stents in the treatment of UEDVT, with or without surgical decompression is uncertain [20].

TREATMENT OF SECONDARY (CATHETER-RELATED) UEDVT

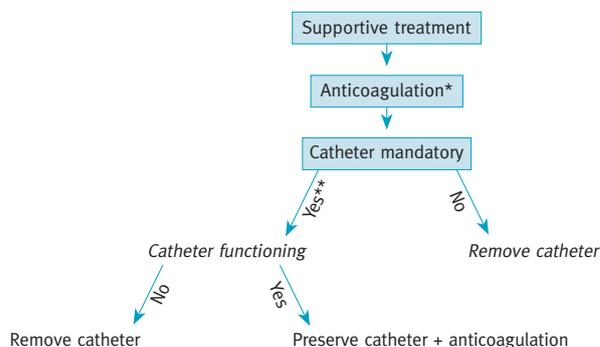
In catheter-related UEDVT, the risk of post-thrombotic syndrome is lower compared to that observed in patients with primary UEDVT [16]. Therefore, the main therapeutic modality for patients with catheter-related UEDVT is anticoagulation (without thrombolysis) for 3–6 months [36]. When the catheter remains in place, or in patients with malignancy, anticoagulation should be considered for a longer period of time [36]. Thrombolytic treatment may be considered only for specific patients with catheter-related UEDVT; that is, those who present with acute severe symptomatic DVT, low bleeding risk, and long life expectancy with required rigorous arm usage [36,37].

The catheter may remain in place if it is mandatory, functioning, well positioned, and not infected. However, if symptoms do not improve with anticoagulation, the catheter should be removed [33]. In cases with limited options for alternative catheter insertion, salvage or opening of the thrombotic catheter with thrombolysis is optional [34]. In non-cancer patients with asymptomatic thrombosis confined to the brachial vein alone, removal of the catheter without anticoagulation may be appropriate [26] [Figure 2].

Routine prophylactic anticoagulation for patients with central catheters is not recommended, even in cancer patients [38]. However, in patients with previous UEDVT, thrombophilia,

Early anticoagulation alone is the treatment of choice for catheter-related thrombosis

Figure 2. Therapeutic approach for catheter-related secondary upper extremity deep vein thrombosis (UEDVT). Supportive treatment should be offered to all patients



*Anticoagulation should be given to all patients for 3 months, unless there is contraindication for anticoagulation treatment (consider umbrella insertion). A longer duration (> 3 months) should be considered if the catheter remains in place. A shorter duration (< 3 months) can be considered following removal of the catheter. Thrombolysis is not routinely recommended for patients with catheter-related UEDVT

**Maintain catheter if it is mandatory and functioning along with anticoagulation treatment. Worsening of symptoms under effective anticoagulation is an indication to repeat ultrasound duplex examination and to consider catheter removal

bulky thoracic cancer, and suboptimal catheter tip position, prophylactic anticoagulation treatment should be considered [39,40].

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Capsule

The good side of ceramides

Tumor growth is enhanced by some members of the ceramide family of lipids and the enzymes that produce them. However, **Gencer** and colleagues found that C18-20 ceramides synthesized by the enzyme CerS4 acted as tumor suppressors. The ceramides prevented a transforming growth factor- β (TGF- β) receptor complex from activating the Shh pathway. CerS4 inhibited metastases from mammary tumors

and the development of the hairloss disorder alopecia in mice. The TGF- β and Shh pathways are challenging to target pharmacologically. These findings suggest that some ceramides may have therapeutic potential against these pathways in various disorders.

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Eitan Israeli

Capsule

An interferon-independent lncRNA promotes viral replication by modulating cellular metabolism

Viruses regulate host metabolic networks to improve their survival. The molecules that are responsive to viral infection and regulate such metabolic changes are hardly known, but are essential for understanding viral infection. **Wang** et al. identified a long noncoding RNA (lncRNA) that is induced by multiple viruses, but not by type I interferon (IFN-I), and facilitates viral replication in mouse and human cells. In vivo deficiency of lncRNA-ACOD1 (a lncRNA identified by its nearest coding gene *Acod1*, aconitate decarboxylase 1) significantly attenuates viral infection through IFN-I-IRF3 (interferon regulatory factor 3)-independent pathways. Cytoplasmic

lncRNA-ACOD1 directly binds the metabolic enzyme glutamic-oxaloacetic transaminase (GOT2) near the substrate niche, enhancing its catalytic activity. Recombinant GOT2 protein and its metabolites could rescue viral replication upon lncRNA-ACOD1 deficiency and increase lethality. This work reveals a feedback mechanism of virus-induced lncRNA-mediated metabolic promotion of viral infection and a potential target for developing broad-acting antiviral therapeutics.

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Capsule

Inflammation-induced IgA+ cells dismantle anti-liver cancer immunity

The role of adaptive immunity in early cancer development is controversial. **Shalapour** et al. showed that chronic inflammation and fibrosis in humans and mice with non-alcoholic fatty liver disease is accompanied by accumulation of liver-resident immunoglobulin-A-producing (IgA+) cells. These cells also express programmed death ligand 1 (PD-L1) and interleukin-10, and directly suppress liver cytotoxic CD8+ T lymphocytes, which prevent emergence of hepatocellular carcinoma and express a limited repertoire of T-cell receptors against tumor-associated antigens.

Whereas CD8+ T-cell ablation accelerates hepatocellular carcinoma, genetic or pharmacological interference with IgA+ cell generation attenuates liver carcinogenesis and induces cytotoxic T-lymphocyte-mediated regression of established hepatocellular carcinoma. These findings establish the importance of inflammation-induced suppression of cytotoxic CD8+ T-lymphocyte activation as a tumor-promoting mechanism.

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